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10/015,824	12/10/2001	Philippe Collas	50195/002002	7491

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,824	COLLAS ET AL.	
	Examin r	Art Unit	
	Thaian N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *3, 10-13, 17, 24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,14-16,18-23 and 31* is/are rejected.

7)☒ Claim(s) *4, 14-16 and 18-23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 6/24/03, Paper No. 8, has been entered. Claim 31 has been added.

Claims 1-31 are pending. Claims 1, 2, 4-9, 14-16, 18-23 and 31 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group I [claims 1, 2, 4, 14-16 and 18-23] in Paper No. 8 is acknowledged. The traversal is on the ground(s) that it would not be unduly unburdensome for the claims of Groups I and VIII to be examined in one application, because the Examiner has stated in the prior Office action that, "[s]ince the product is not allowable, restriction is proper between said method of making and method of using." Applicants note that no reason has been provided by the Examiner for the unpatentability of the cells produced using the claimed method and respectfully assert that such cells are patentable.

In response, the Examiner submits that the prior reasoning was in error. Inventions I and VIII are to distinct methods, which have materially different method steps and have different technical considerations. The methods of Invention I are directed to methods of reprogramming a cell by incubating a nucleus from a donor cell with a reprogramming media under conditions that allow the removal of a factor from the nucleus or the addition of a factor from said

reprogramming media to said nucleus, and inserting the nucleus or a chromatin mass formed from the nucleus into a recipient cell or cytoplast, thereby forming a reprogrammed cells. The methods of Invention VIII are directed to methods of treating or preventing a disease, disorder or condition in a mammal comprising incubating a nucleus or chromatin mass from a donor cell with a reprogramming media under conditions that allow the removal of a factor from the nucleus or the addition of a factor from said reprogramming media to said nucleus, and inserting the nucleus or a chromatin mass formed from the nucleus into a recipient cell or cytoplast and administering the resulting reprogrammed cell to a mammal. The two inventions are distinct because cells of Invention I can be used in methods distinct from that of Invention VIII, for example, utilizing the reprogrammed cell to produce a nuclear transfer unit, which can be further used to produce an animal. The differences between Inventions I and VIII are further underscored by their divergent classification and independent search status.

Because Inventions I and VIII are distinct for the reasons given above, and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicants' argue that the same literature search that can be used to examine claims directed to methods of reprogrammed cells and methods of administering the resulting reprogrammed cells to a mammal, and thus, it would not be an undue burden on the Examiner to evaluate the methods of making and

using these cells as one group. Applicants argue that the same argument applies for Examiner's Groups II and IX and submit that Groups I, II, VIII and IX should be examined together. See pp. 4-5 of Applicant's Response.

This is not found persuasive for the reasons stated above, with regard to why Inventions I and VIII are distinct. By applying the same reasoning as stated above, Inventions II and IX are to distinct methods, which have materially different methods steps and different technical considerations. For example, the reprogrammed cells of Invention II can be used in a nuclear transfer method to produce a nuclear transfer unit, which can be further used to produce an animal. The differences between Inventions II and IX are further underscored by their divergent classification and independent search status.

Applicants note that newly added claim 31 falls with Examiner's Group I includes cells produced by the methods of claim 1 or 2. After further consideration, the Examiner agrees to examine claim 31 and the cells recited in Groups IV-VII with Group I.

Claims 3, 10-13, 17, 24-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Accordingly, claims 1, 2, 4-9, 14-16, 18-23 and 31 are under current examination.

Claim Objections

Claims 4, 14-16 and 18-23 objected to because of the following informalities:

The claims refer to claims that have been withdrawn from examination. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 14-16 and 18-23 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does

not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The claims are directed to methods of reprogramming a cell, said method comprising the steps of incubating a nucleus from a donor cell with a reprogramming media under conditions that allow the removal of a factor from said nucleus or the addition of a factor from said reprogramming media to said nucleus, and inserting said nucleus or a chromatin mass formed from the nucleus into a recipient cell or cytoplast, thereby forming a reprogrammed cell. The specification fails to provide adequate written description for what factors would be removed from a donor nucleus or added from the reprogramming media. The specification teaches broadly that factors that may be included in the reprogramming media can include DNA methyltransferase, histone deacetylase, histone, nuclear laminin, transcription factor(s), for example [see p. 12, lines 6-9]; and that "the addition of a factor" means the binding of a factor to chromatin, a chromosome, or a component of the nuclear envelope [see p. 18, lines 11-16]. The specification further teaches that the term, "removal of a factor" means the dissociation of a factor from chromatin, a chromosome, or a component of the nuclear envelope [see p. 18, lines 17-22]. However, the specification fails to describe with particularity, the addition or removal of factor, which when used in the claimed methods would produce a reprogrammed cell, to indicate that Applicants had possession of the claimed invention.

The claimed invention *as a whole* is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

In the instant case, the claimed embodiment of *"a factor"* lacks a written description. The specification fails to describe what factor(s) fall into this genus when used as claimed; the skilled artisan cannot envision such factors which, when used as claimed, would result in a reprogrammed cell. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, as no factors, which would be removed or added into the donor nucleus to form a reprogrammed cell, were described, they do meet the written description provision of 35 U.S.C. § 112.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-9, 14-16, 18-23 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of reprogramming a cell, said method comprising the steps of incubating a nucleus from a donor cell with a reprogramming media under conditions that allow the removal of a factor from said

nucleus or the addition of a factor from said reprogramming media to said nucleus, and inserting said nucleus or chromatin mass formed from said nucleus into a recipient cell or cytoplast, thereby forming a reprogrammed cell and cells produced by the method, wherein the cell expresses a combination of two or more endogenous mRNA molecules or endogenous proteins that is not expressed in a naturally-occurring cell.

The specification teaches methods for converting cells into a desired cell type by incubating the nucleus or chromatin mass from a donor cell with a reprogramming media under conditions that allow nuclear or cytoplasmic components, such as transcription factors, to be added to, removed from, the nucleus or chromatin mass. See p. 1, lines 25-29. The specification teaches that the reprogramming media can be an interphase reprogramming media from cells synchronized in one or more phases of the cell cycle. The reprogramming media may also be an extract formed from cells synchronized in mitosis or from unsynchronized cells. See p. 11, lines 24-29. The specification teaches the preparation of reprogramming media made from interphase cultured cells, wherein isolated, purified nuclei are resuspended in the reprogrammed media and an ATP generating system added to the extract to promote active uptake of nuclear components by the exogenous nuclei. This reaction is incubated for up to two hours and then the reprogrammed nuclei are then purified away from the extract and then used in nuclear transfer methods. See Example 1, pp. 35-42. The specification

teaches that in a two-step reprogramming method, nuclei are isolated from interphase cells, incubated in amitotic extract, and a solution to induce the nucleuar envelope breakdown and formation of chromatin masses. These chromatin masses are then incubated with an interphase reprogramming extract to promote the formation of nuclear membranes. The reprogrammed nuclei are then isolated from the extract and inserted into recipient cells or cytoplasts of the appropriate cell type. See Example 2.

The specification teaches methods of reprogramming using an activated T-cell extract, which is based upon functional differences between resting and activated T-cells. The specification teaches that cell extracts from activated human T-cells were used to induce nuclear localization of transcription factors in unactivated human T-cells, B-cells, human fibroblasts and HeLa cells. The specification teaches that activated T-cell extract was prepared and donor nuclei from resting human T-cells, B-cells, fibroblasts, HUVEC, HeLa and NT2 nuclei were isolated and purified, see pp. 51-52. The nuclei were then incubated in the T-cell extract and then purified away from the extract by centrifugation. The specification teaches that the T-cell specific transcription factor, NFAT, was imported into the nuclei exposed to the stimulated extract [see p. 52, lines 4-5 and Figure 3A and 6A]. The specification teaches that the ability of other transcription factors from the extract to migrate into the nuclei of T-cells, B-cells, fibroblasts and HeLa cells was determined. See Example 4. The specification teaches that nuclear

reprogramming is evidenced by the transcriptional activation of a silent gene, IL-2 , which can be induced in purified intact nuclei. See p. 59, lines 1-5. The specification teaches the reprogramming of fibroblasts using an activated T-cell extract. Particularly, stimulated T-cell reprogramming extract was prepared and incubated with fibroblast nuclei. At the end of the incubation, either the nuclei were purified by sedimentation, or total RNA extracted for RT-PCR. The specification teaches the increase in ATPase levels, hyperacetylation of histone H4, and the expression of IL-2, which the specification teaches is a stringent indicator of nuclear reprogramming. See p. 62.

The specification fails to enable the instant invention because the specification fails to teach or provide guidance for the starting materials, for example, factors present in the reprogramming extract that would be used to practice the claimed methods. The specification provides teachings to show that by exposing nuclei to the extracts of the claimed invention, there is an increase of expression in various genes; however, the specification fails to show that the cells that are produced by the claimed methods are in any way reprogrammed. The specification provides a general definition of a "reprogramming media" – a solution that allows the removal of a factor from a nucleus, chromatin mass, or chromosome or the addition of a factor from the solution to the nucleus, chromatin mass, or chromosome – and further, that by incubation of a nucleus in the reprogramming media alters the phenotype of the cell containing the reprogrammed chromatin

mass or nucleus relative to the phenotype of the donor cell. See p. 17, lines 11-22. The specification teaches that the cells of the instant invention are converted into a desired cell type. See p. 1, lines 12-14. However, the specification fails to show that the cells, as taught by the instant specification, when incubated with a reprogramming media, are indeed converted into a desired cell type, *i.e.*, reprogrammed. The showing of increase or decrease of protein or gene expression fails to show that the cells are a different type of cell. It is well-known in the art that reprogramming is a complex mechanism that is not well understood and the state of the art of reprogramming cells supports that the it is unpredictable and undeveloped. For example, Wade and Kikyo [**Eur. J. Biochem.**, 269:2284-2284 (2002)] state that,

> Recent successes in mammalian cloning with differentiated adult nuclei strong indicate that oocyte cytoplasm contains unidentified remarkable reprogramming activities with the capacity to erase the previous memory of cell differentiation. At the heart of this nuclear reprogramming lies chromatin remodeling as chromatin structure and function define cell differentiation through regulation of the transcriptional activities of the cells. See *Abstract.*

They further discuss chromatin modification in *Xenopus* and mammalian cloning, stating that, "[N]ewly identified histone methylation and heterochromatin formation as an entirely unexplored filed of chromatin modification involved in

nuclear cloning." See p. 2284, 2nd column, 1st ¶. With regard to histone methylation, they state that it is unknown if the methylation of histones of arginine or lysine residues is reversible and provide several possible fates for histones methylated at arginine and lysine residues in NT experiments, stating that, "Deciphering the developmental appearance of histone methlyation, the reversibility of this modification, and whether erasure of this epigenetic mark impacts the outcome of nuclear transfer remain important challenges for the future." See p. 2286, 1st column, 2nd ¶. Wade and Kikyo teach that reprogramming of cells is unpredictable in stating that, "Improved understanding of the molecular mechanisms of nuclear programming will potentially lead to an enhanced ability to engineer cells with desired traits for therapeutic purposes without the use of human embryonic materials." See p. 2286, 2nd column, last sentence.

Further, Kikyo and Wolffe [J. Cell Sci., 113:11-20 (2000)] discuss the mechanisms involved in reprogramming nuclear transfer stating that, "An understanding of these mechanisms not only will potentially provide insight into the significance of epigenetic events in establishing a developmental and differentiative program, but also might suggest new approaches towards improving the efficiency and success of nuclear transfer procedures." See p. 11, 2nd column, 1st ¶. They teach that although progress has been made in understanding the mechanisms [such as transcriptional controls] involved in the reprogramming of a somatic nuclei by egg cytoplasm, more research is required to specifically

understand the processes involved in reprogramming of somatic cells. See pp. 16-17, *Outlook*.

The unpredictability of reprogramming cells in nuclear transfer methods is further supported by Gurdon *et al.* [PNAS, August 14, 2003, e-publication, pp. 1-4] who review the state of the art of nuclear reprogramming. They teach that work with both amphibian and mammals has shown that nuclear transfer experiments are inefficient, "Quantitatively incomplete/incorrect reprogramming of gene expression has been found in both amphibians and mammalian cloned embryos, and it is suggested that this may affect development." See p. 3, 1st column, 2nd ¶. They state that, "In conclusion, there is no definite explanation for the high frequency with which nuclei transplanted from differentiated or adult cells fail to elicit any cleavage of devlopemnt of recipient eggs." See p. 3, 3rd ¶. They teach that further research needs to be done to elicit the specific mechanisms and molecules involed in reprogramming. See p. 4, 2nd column, last ¶.

As such, in light of the state of the art of reprogramming, the specification fails to provide teachings or guidance to show that the cells of the invention are indeed reprogrammed. The mere showing of gene expression is not sufficient evidence to show that the cells produced by the claimed method are reprogrammed, as methods well known in the art can change gene expression. For example, introduction of cells to cytokines can turn on gene expression. Note that the product

claims have been included in this rejection because they encompass reprogrammed cells made by the claimed method.

As such, in view of the specification's lack of teaching or guidance with regard to factors that are either removed from the donor nucleus, or addition of factors from the reprogramming media, the lack of teaching or guidance to show that the cells resulting from the claimed method would be reprogrammed, the unpredictable and undeveloped state of the art with regard to reprogramming, it would have required undue experimentation for one of skill in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4, as written, is unclear. The claim recites that the cell expresses a combination of two or more endogenous mRNA molecules or endogenous proteins that is not expressed in a naturally-occurring cell. It is unclear if it is the mRNA molecules or the proteins that are not expressed in the naturally-occurring cell. Furthermore, the term "naturally occurring" is unclear. For example, many endogenous mRNAs are turned on and off during the development of a cell, yet the cell would be "naturally-occurring".

Claim 4-9 and 31, as written, are indefinite because the term "fibroblast-specific proteins" is not specifically defined. This is unclear, as fibroblasts express proteins that many other cells express, and other cells express proteins that are additionally expressed in fibroblasts.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by DiBerardino *et al.* [PNAS, 83:8231-8234, Nov. 1986].

The claims are directed to methods of reprogramming a cell, said method comprising the steps of incubating a nucleus from a donor cell with a reprogramming media under conditions that allow the removal of a factor from said nucleus or the addition of a factor from said reprogramming media to said nucleus, and inserting said nucleus or chromatin mass formed from said nucleus into a recipient cell or cytoplast, thereby forming a reprogrammed cell.

DiBerardino teach the generation of feeding tadpoles that were cloned from *Rana* erythrocyte nuclei. Particularly, they teach that the membranes of donor erythrocytes were broken down by osmotic rupture and the contents of 1-10 cells

were injected into oocytes. Approximately 24 hours after the oocytes completed maturation, they were activated parthenogenetically, and the nuclear transplants were observed through at least the first three cleavage stages. The resulting cells were used as donor cells in a nuclear transplantation method. See *Materials & Methods.*

Note that the specification broadly defines a reprogramming media as a As such, the incubation of frog erythrocyte nuclei into oocytes would fulfill the limitations of the claim invention.

Accordingly, DiBerardino anticipate the claimed invention.

Claims 1, 4, and 21-23 rejected under 35 U.S.C. 102(b) as being anticipated by Schnieke *et al.* [Science, 278:2130-2133 (1997)].

The claims are directed to reprogrammed cells and methods of reprogramming a cell comprising incubating a nucleus from a donor cell with a reprogramming media under conditions that allow the removal of a factor from the nucleus, or the addition of a factor from the media to the nucleus, and inserting the nucleus or a chromatin mass formed from said nucleus into a recipient cell or cytoplast.

Schnieke teach the generation of transgenic sheep produced by the transfer of fetal fibroblast nuclei into enucleated oocytes. Particularly they teach that Poll Dorset fetal fibroblasts [PDFF2] were transfected and cultured. The cell nuclei

were then transferred into enucleated oocytes. See p. 2131, col. 2-3. Note that Schnieke teaches the claimed invention because the claimed mechanism is not defined by the specification; in particular, the factors that are removed or added are not specifically defined by the specification. As such, Schnieke's teaching of the incubation of the nuclei prior to nuclear transfer and the consequent birth of a live born sheep anticipates the claimed invention.

Claims 5 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Sun *et al.* [**Cancer Gene Therapy**, 5(2):110-118, (1998)].

The claims are directed to cells that express a T-cell receptor or IL-2 and one or more fibroblast-specific proteins.

The claims are product-by-process claims. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re* Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re* Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing *In re* Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685

(1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Sun teach LM cells, which are mouse fibroblasts cells which secrete interleukin-2. See *Abstract* and *Materials & Methods*, p. 111, 2nd column, 1st ¶. As fibroblast cells would express fibroblast-specific proteins, Sun anticipate the claimed invention.

Claims 4, 6 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Li *et al.* [**Eur. J. Biochem.**, 262:211-217 (May 1999)].

The claims are directed to cells that express a neurofilament protein and one or more fibroblast-specific proteins. Note that the claims are product-by-process claims. See *supra.*

Li teach that NIH 3T3 cells were co-transfected with a NF-M [high molecular weight neurofilament protein] construct and a constitutively active form of mitogen-activated ERK activating kinase [MEK1]. See Materials & Methods, p. 212. Expression of NF-M and MEK1 was analyzed. See Figure 2. Note that the fibroblasts would inherently express fibroblast-specific proteins.

As Li teach fibroblasts expression NF-M, they anticipate the claimed invention.

Claims 7 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson *et al.* [U.S. Pat. No. 5,654,183, published August 5, 1997].

The claims are directed to cells that express a neurofilament protein NF200 and are immortalized. Note that the claims are product-by-process claims. See *supra.*

Anderson teach multipotent mammalian neural stem cells. They teach that neurofilament proteins, such as NF200 can be expressed in the cells. See col. 12, lines 37-64. They teach methods of immortalizing the cell lines [see col. 7-8, bridging ¶ and col. 17-18, bridging ¶].

Accordingly, Anderson teach the claimed invention.

Claims 4, 8 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by de Anta *et al.* [Histol. Histopathol., 12(1):33-41, (1997)].

The claims are directed to cells that express Oct4 or alkaline phosphatase and one or more fibroblast-specific proteins. Note that the claims are product-by-process claims. See *supra.*

de Anta teach that k-FGF is a fibroblast growth factor. They teach the expression of Oct-4 and kFGF in embryonal carcinoma and ES cells. See *Summary*. Accordingly, de Anta anticipate the claimed invention.

Claims 9 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Risau *et al.* [**Development**, 102:471-478 (1988)].

The claims are directed to cells produced using the method of claims 1 or 2, wherein the cell expresses a combination of two or more endogenous mRNA molecules or endogenous proteins that is not expressed in a naturally-occuring cell; a cell that expresses one or more fibroblast-specific proteins and grows in aggregates, forms colonies, or forms embryoid bodies.

Note that the claims are product-by-process claims. See *supra*.

Risau teach ES cells that are mouse blastocyst-derived. These embryoid bodies of the ES cells were then transplanted into recipient mice. The embryoid bodies were then assayed for expression of various growth factors. See Methods & Materials. It was found that the embryoid bodies expressed fibroblast growth factor. See p. 474, 2nd column, 2nd ¶. As Risau teach ES cells that express one or more fibroblast-specific proteins and form embryoid bodies, they anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)-872-9306.

Deborah D Crouch

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